

Patent claims

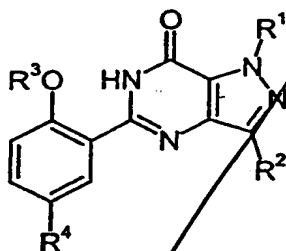
1. A combination preparation, comprising as pharmaceutically active ingredients at least one active compound component A and at least one active compound component B, characterized in that the active compound component A is a PDE inhibitor, preferably a cGMP PDE inhibitor, and the active compound component B is an antilipemic.
2. The combination preparation as claimed in claim 1 for treating sexual dysfunction in men or women.
3. The combination preparation as claimed in claim 2 for treating erectile dysfunction.
4. The combination preparation as claimed in any of claims 1 to 3, characterized in that the two active compound components A and B are used either simultaneously or successively.
5. The combination preparation as claimed in any of claims 1 to 4, characterized in that the active compound components A and B are present as a functional unit, in particular in the form of a mixture, a mix or a blend.
6. The combination preparation as claimed in any of claims 1 to 4, characterized in that the active compound components A and B are (spatially) separated, in particular as a kit-of-parts.
7. The combination preparation as claimed in any of claims 1 to 6, characterized in that the antilipemic (active compound component B) is selected from the group consisting of (a) HMG-CoA-reductase inhibitors; (b) squalene synthase inhibitors; (c) bile acid sequestrants; (d) fibric acid and its derivatives; (e) nicotinic acid and its analogs; (f) ω 3-fatty acids.
8. The combination preparation as claimed in claim 7, characterized in that the

antilipemic (active compound component B) is an HMG-CoA-reductase inhibitor and is in particular selected from the group of the statins, preferably from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, itavastatin, simvastatin and (+)-(3R,5S)-bis-(7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methanesulfonylamino)-pyrimidin-5-yl)-3,5-dihydroxy-6(E)-heptenoic acid, and their respective salts, hydrates, alkoxides, esters and tautomers.

9. The combination preparation as claimed in claim 8, characterized in that the antilipemic (active compound component B) is atorvastatin or its salt, hydrate, alkoxide, ester and tautomer.

10. The combination preparation as claimed in claim 8, characterized in that the antilipemic (active compound component B) is cerivastatin or its salt, hydrate, alkoxide, ester and tautomer.

11. The combination preparation as claimed in any of claims 1 to 10, characterized in that the PDE inhibitor (active compound component A) is a cGMP PDE inhibitor and is in particular selected from the group consisting of pyrazolopyrimidones of the general formula below



in which

R¹ represents hydrogen; C₁-C₃-alkyl; C₁-C₃-perfluoroalkyl; or C₃-C₅-cycloalkyl;

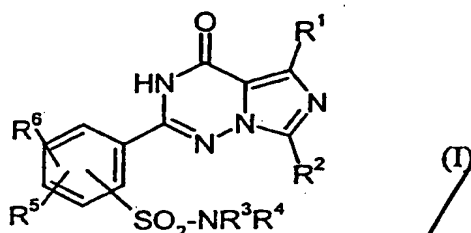
R² denotes hydrogen; C₁-C₆-alkyl, optionally substituted by C₃-C₆-cycloalkyl; C₁-C₆-perfluoroalkyl; or C₃-C₆-cycloalkyl;

R³ is C₁-C₆-alkyl, optionally substituted by C₃-C₆-cycloalkyl; C₁-C₆-perfluoroalkyl; C₃-C₅-cycloalkyl; C₃-C₆-alkenyl; or C₃-C₆-alkinyl;

- R^4 represents C_1 - C_4 -alkyl, optionally substituted by OH, NR^5R^6 , CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 -alkenyl, optionally substituted by CN, $CONR^5R^6$ or CO_2R^7 ; C_2 - C_4 -alkanoyl, optionally substituted by NR^5R^6 ; (hydroxy)- C_2 - C_4 -alkyl, optionally substituted by NR^5R^6 , (5
(C_2 - C_3 -alkoxy)- C_1 - C_2 -alkyl, optionally substituted by OH or NR^5R^6 , CO_2R^7 ; halogen; NR^5R^6 , $NHSO_2NR^5R^6$; $NHSO_2R^8$; $SO_2NR^9R^{10}$; or phenyl, pyridyl, pyrimidinyl, imidazolyl, oxazolyl, thiazolyl, thienyl or triazolyl, each of which is optionally substituted by methyl;
- 10 R^5 and R^6 each independently of one another denote hydrogen or C_1 - C_4 -alkyl; or together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{11})$ -piperazinyl or imidazolyl group, where this group is optionally substituted by methyl or OH;
- 15 R^7 is hydrogen or C_1 - C_4 -alkyl;
- R^8 represents C_1 - C_3 -alkyl, optionally substituted by NR^5R^6 ;
- 20 R^9 and R^{10} together with the nitrogen atom to which they are attached form a pyrrolidinyl, piperidino, morpholino, 4- $N(R^{12})$ -piperazinyl group, where this group is optionally substituted by C_1 - C_4 -alkyl, C_1 - C_3 -alkoxy, $NR^{13}R^{14}$ or $CONR^{13}R^{14}$;
- 25 R^{11} denotes hydrogen, C_1 - C_3 -alkyl, optionally substituted by phenyl; (hydroxy)- C_2 - C_3 -alkyl; or C_1 - C_4 -alkanoyl;
- 30 R^{12} is hydrogen, C_1 - C_6 -alkyl, (C_1 - C_3 -alkoxy)- C_2 - C_6 -alkyl; (hydroxy)- C_2 - C_6 -alkyl; ($R^{13}R^{14}N$)- C_2 - C_6 -alkyl; ($R^{13}R^{14}NOC$)- C_1 - C_6 -alkyl; $CONR^{13}R^{14}$; $CSNR^{13}R^{14}$, or $C(NH)NR^{13}R^{14}$; and
- R^{13} and R^{14} each independently of one another represent hydrogen; C_1 - C_4 -alkyl; (C_1 - C_3 -alkoxy)- C_2 - C_4 -alkyl; or (hydroxy)- C_2 - C_4 -alkyl;

and their respective salts, hydrates, alkoxides and tautomers.

12. The combination preparation as claimed in any of claims 1 to 10,
 5 characterized in that the PDE inhibitor (active compound component A) is a
 cGMP PDE inhibitor and is in particular selected from the group consisting
 of 2-phenyl-substituted imidazotriazinones of the general formula



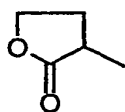
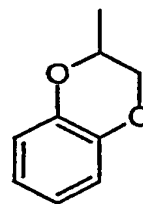
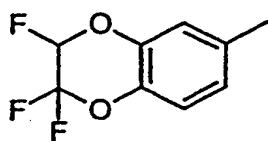
in which

10 R^1 represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms;

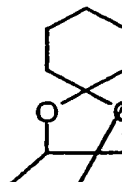
15 R^2 represents straight-chain alkyl having up to 4 carbon atoms;

20 R^3 and R^4 are identical or different and represent hydrogen or represent straight-chain or branched alkenyl or alkoxy having in each case up to 8 carbon atoms, or represent a straight-chain or branched alkyl chain having up to 10 carbon atoms which is optionally interrupted by an oxygen atom and which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of trifluoromethyl, trifluoromethoxy, hydroxyl, halogen, carboxyl, benzyloxycarbonyl, straight-chain or branched alkoxy carbonyl having up to 6 carbon atoms and/or by radicals of the formulae $-SO_3H$, $-(A)_a-NR^7R^8$, $-O-CO-NR^7R^8$, $-S(O)_b-R^9$, $-P(O)(OR^{10})(OR^{11})$,

25



and/or



in which

a and b are identical or different and represent a number 0 or 1,

5

A represents a radical CO or SO₂,

R⁷, R^{7'}, R⁸ and R^{8'} are identical or different and represent hydrogen, or represent cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms, a 5- to 6-membered unsaturated, partially unsaturated or saturated optionally benzo-fused heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, where the abovementioned ring systems are optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, carboxyl, halogen, straight-chain or branched alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms or by a group of the formula -(SO₂)_c-NR¹²R¹³,

10

15

20

in which

c represents a number 0 or 1,

R^{12} and R^{13} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 5 carbon atoms,

or

R^7 , $R^{7'}$, R^8 and $R^{8'}$ represent straight-chain or branched alkoxy having up to 6 carbon atoms, or

represent straight-chain or branched alkyl having up to 8 carbon atoms which is optionally mono- or polysubstituted by identical or different substituents from the group consisting of hydroxyl, halogen, aryl having 6 to 10 carbon atoms, straight-chain or branched alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, or by a group of the formula $-(CO)_d-NR^{14}R^{15}$,

in which

R^{14} and R^{15} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

and

d represents a number 0 or 1,

or

R^7 and R^8 and/or $R^{7'}$ and $R^{8'}$ together with the nitrogen atom form a 5- to 7-membered saturated heterocycle which may optionally contain a further heteroatom from the group consisting of S and O or a radical of the formula $-NR^{16}$,

in which

R^{16} represents hydrogen, aryl having 6 to 10 carbon atoms, benzyl, a 5- to 7-membered aromatic or saturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, which heterocycle is optionally substituted by methyl, or
5 represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl,

R^9 represents aryl having 6 to 10 carbon atoms, or
10 represents straight-chain or branched alkyl having up to 4 carbon atoms,

R^{10} and R^{11} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

15 and/or the alkyl chain listed above under R^3/R^4 is optionally substituted by cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms or by a 5- to 7-membered partially unsaturated, saturated or unsaturated optionally benzo-fused heterocycle which may contain up to 4 heteroatoms from the group consisting of S, N; O or a radical of the formula $-NR^{17}$,

20 in which

R^{17} represents hydrogen, hydroxyl, formyl, trifluoromethyl, straight-chain or branched acyl or alkoxy having in each case up to 4 carbon atoms,
25 or represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl and straight-chain or branched alkoxy having up to 6 carbon atoms,

30 and where aryl and the heterocycle are optionally mono- to polysubstituted by identical or different substituents from the group consisting of nitro, halogen, $-SO_3H$, straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms, hydroxyl, trifluoromethyl, trifluoromethoxy and/or by a radical

of the formula $-\text{SO}_2\text{NR}^{18}\text{R}^{19}$,

in which

5 R^{18} and R^{19} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

and/or

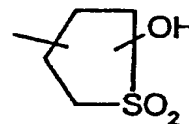
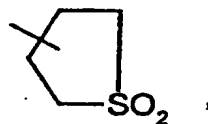
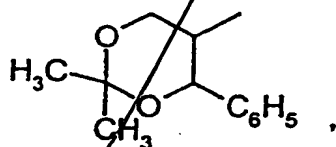
10 R^3 or R^4 represent a group of the formula $-\text{NR}^{20}\text{R}^{21}$,

in which

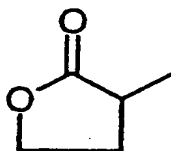
15 R^{20} and R^{21} have the meaning of R^{18} and R^{19} given above and are identical to or different from this meaning

and/or

20 R^3 or R^4 represent adamantyl, or represent radicals of the formulae



or



25 or represent cycloalkyl having 3 to 8 carbon atoms, aryl having 6 to 10 carbon atoms or represent a 5- to 7-membered partially unsaturated, saturated or unsaturated optionally benzo-fused

heterocycle which may contain up to 4 heteroatoms from the group consisting of S, N; O or a radical of the formula $-NR^{22}$,

in which

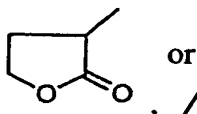
R^{22} has the meaning of R^{16} given above and is identical to or different from this meaning, or represents carboxyl, formyl or straight-chain or branched acyl having up to 5 carbon atoms,

and where cycloalkyl, aryl and/or the heterocycle are optionally mono- to polysubstituted by identical or different substituents from the group consisting of halogen, triazolyl, trifluoromethyl, trifluoromethoxy, carboxyl, straight-chain or branched acyl or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro, and/or by groups of the formulae $-SO_3H$, $-OR^{23}$, $(SO_2)_eNR^{24}R^{25}$, $-P(O)(OR^{26})(OR^{27})$,

in which

e represents a number 0 or 1,

R^{23} represents a radical of the formula



represents cycloalkyl having 3 to 7 carbon atoms, or represents hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms which is optionally substituted by cycloalkyl having 3 to 7 carbon atoms, benzyloxy, tetrahydropyranyl, tetrahydrofuranyl, straight-chain or branched alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms, carboxyl, benzyloxycarbonyl or phenyl which for its part may be mono- to polysubstituted by identical or

different substituents from the group consisting of straight-chain or branched alkoxy having up to 4 carbon atoms, hydroxyl and halogen,

and/or alkyl is optionally substituted by radicals of the formulae $-\text{CO}-\text{NR}^{28}\text{R}^{29}$ or $-\text{CO}-\text{R}^{30}$,

in which

R^{28} and R^{29} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 8 carbon atoms, or

R^{28} and R^{29} together with the nitrogen atom form a 5- to 7-membered saturated heterocycle which may optionally contain a further heteroatom from the group consisting of S and O,

and

R^{30} represents phenyl or adamantyl,

R^{24} and R^{25} have the meaning of R^{18} and R^{19} given above and are identical to or different from this meaning,

R^{26} and R^{27} have the meaning of R^{10} and R^{11} given above and are identical to or different from this meaning

and/or cycloalkyl, aryl and/or the heterocycle are optionally substituted by straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl, carboxyl, by a 5- to 7-membered heterocycle having up to 3 heteroatoms from the group consisting of S, N and O or by groups of the formula $-\text{SO}_2-\text{R}^{31}$, $\text{P}(\text{O})(\text{OR}^{32})(\text{OR}^{33})$ or $-\text{NR}^{34}\text{R}^{35}$,

in which

R^{31} is hydrogen or has the meaning of R^9 given above and is identical to or different from this meaning,

5 R^{32} and R^{33} have the meaning of R^{10} and R^{11} given above and are identical to or different from this meaning,

10 R^{34} and R^{35} are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms which is optionally substituted by hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms, or

15 R^{34} and R^{35} together with the nitrogen atom form a 5- to 6-membered saturated heterocycle which may contain a further heteroatom from the group consisting of S and O or a radical of the formula $-NR^{36}$,

in which

20 R^{36} represents hydrogen, hydroxyl, straight-chain or branched alkoxycarbonyl having up to 7 carbon atoms or straight-chain or branched alkyl having up to 5 carbon atoms which is optionally substituted by hydroxyl,

or

25 R^3 and R^4 together with the nitrogen atom form a 5- to 7-membered unsaturated or saturated or partially unsaturated optionally benzo-fused heterocycle which may optionally contain up to 3 heteroatoms from the group consisting of S, N, O or a radical of the formula $-NR^{37}$,

30

in which

R^{37} represents hydrogen, hydroxyl, formyl, trifluoromethyl, straight-chain

or branched acyl, alkoxy or alkoxycarbonyl having in each case up to 4 carbon atoms,

or represents straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, trifluoromethyl, carboxyl, straight-chain or branched alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms or by groups of the formula - (D)_f-NR³⁸R³⁹, -CO-(CH₂)_g-O-CO-R⁴⁰, -CO-(CH₂)_h-OR⁴¹ or -P(O)(OR⁴²)(OR⁴³),

in which

g and h are identical or different and represent a number 1, 2, 3 or 4,

and

f represents a number 0 or 1,

D represents a group of the formula -CO or -SO₂,

R³⁸ and R³⁹ are identical or different and have the meaning of R⁷ and R⁸ given above,

R⁴⁰ represents straight-chain or branched alkyl having up to 6 carbon atoms,

R⁴¹ represents straight-chain or branched alkyl having up to 6 carbon atoms,

R⁴² and R⁴³ are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

or

R^{37} represents a radical of the formula $-(CO)_i-E$,

in which

i represents a number 0 or 1,

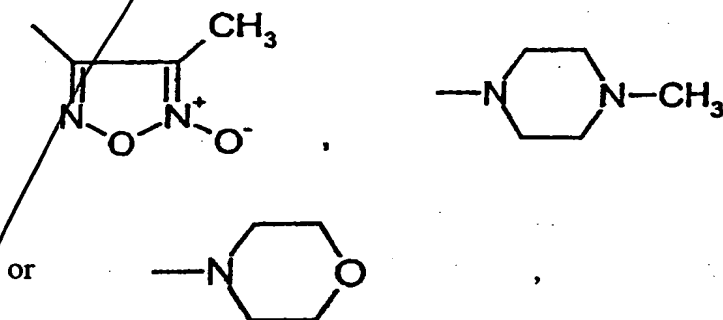
E represents cycloalkyl having 3 to 7 carbon atoms or benzyl, represents aryl having 6 to 10 carbon atoms or a 5- to 6-membered aromatic heterocycle having up to 4 heteroatoms from the group consisting of S, N and O, where the ring systems listed above are optionally mono- to polysubstituted by identical or different substituents from the group consisting of nitro, halogen, $-SO_3H$, straight-chain or branched alkoxy having up to 6 carbon atoms, hydroxyl, trifluoromethyl, trifluoromethoxy or by a radical of the formula $-SO_2-NR^{44}R^{45}$,

in which

R^{44} and R^{45} have the meaning of R^{18} and R^{19} given above and are identical to or different from this meaning,

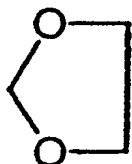
or

E represents radicals of the formulae



and the heterocycle listed under R^3 and R^4 , which is formed together

with the nitrogen atom, is optionally mono- to polysubstituted by identical or different substituents, if appropriate also geminally, by hydroxyl, formyl, carboxyl, straight-chain or branched acyl or alkoxycarbonyl having in each case up to 6 carbon atoms, nitro and groups of the formulae $-P(O)(OR^{46})(OR^{47})$,



$=NR^{48}$ or $-(CO)_jNR^{49}R^{50}$,

in which

R^{46} and R^{47} have the meaning of R^{10} and R^{11} given above and are identical to or different from this meaning,

R^{48} is hydroxyl or straight-chain or branched alkoxy having up to 4 carbon atoms,

j is a number 0 or 1,

and

R^{49} and R^{50} are identical or different and have the meaning of R^{14} and R^{15} given above,

and/or the heterocycle listed under R^3 and R^4 , which is formed together with the nitrogen atom, is optionally substituted by straight-chain or branched alkyl having up to 6 carbon atoms which is optionally mono- to polysubstituted by identical or different substituents from the group consisting of hydroxyl, halogen, carboxyl, cycloalkyl or cycloalkyloxy having in each case 3 to 8 carbon atoms, straight-chain or branched alkoxy or alkoxycarbonyl having in each case up to 6 carbon atoms or by a radical of the formula $-SO_3H$, $-NR^{51}R^{52}$ or $P(O)OR^{53}OR^{54}$,

in which

5 R^{51} and R^{52} are identical or different and represent hydrogen, phenyl, carboxyl, benzyl or straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms,

10 R^{53} and R^{54} are identical or different and have the meaning of R^{10} and R^{11} given above,

and/or the alkyl is optionally substituted by aryl having 6 to 10 carbon atoms which for its part may be mono- to polysubstituted by identical or different substituents from the group consisting of halogen, hydroxyl, straight-chain or branched alkoxy having up to 6 carbon atoms, or by a group of the formula $-NR^{51'}R^{52'}$,

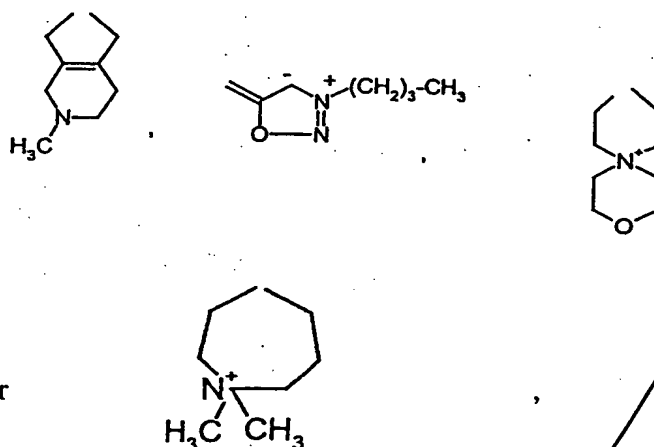
in which

20 $R^{51'}$ and $R^{52'}$ have the meaning of R^{51} and R^{52} given above and are identical to or different from this meaning,

25 and/or the heterocycle listed under R^3 and R^4 , which is formed together with the nitrogen atom, is optionally substituted by aryl having 6 to 10 carbon atoms or by a 5- to 7-membered saturated, partially unsaturated or unsaturated heterocycle having up to 3 heteroatoms from the group consisting of S, N and O, if appropriate also attached via an N-function, where the ring systems for their part may be substituted by hydroxyl or by straight-chain or branched alkyl or alkoxy having in each case up to 6 carbon atoms,

30 or

R^3 and R^4 together with the nitrogen atom form radicals of the formulae



R⁵ and R⁶ are identical or different and represent hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, hydroxyl or represent straight-chain or branched alkoxy having up to 6 carbon atoms.

5 and their respective salts, hydrates, alkoxides and tautomers.

13. The combination preparation as claimed in any of claims 1 to 10, characterized in that the PDE inhibitor (active compound component A) is a cGMP PDE inhibitor and in particular is selected from the group consisting of (a) 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one (sildenafil) and its salts, hydrates, alkoxides and tautomers; and (b) 2-[2-ethoxy-5-(4-ethylpiperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f]-[1,2,4]-triazin-4-one and its salts, hydrates, alkoxides and tautomers.

14. The combination preparation as claimed in claim 13, in that the PDE inhibitor (active compound component A) is 5-[2-ethoxy-5-(4-methyl-1-piperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo-[4,3-d]-pyrimidin-7-one citrate (sildenafil citrate, ViagraTM) or 2-[2-ethoxy-5-(4-ethylpiperazine-1-sulfonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one hydrochloride trihydrate.

15. The use of antilipemics for enhancing the activity of PDE inhibitors, in

particular cGMP PDE inhibitors.

16. The use as claimed in claim 15 in the treatment of sexual dysfunction in men and women, in particular in the treatment of erectile dysfunction.
- 5 17. The use as claimed in claim 15 or 16, characterized in that the antilipemic and the PDE inhibitor are used either simultaneously or else successively.
- 10 18. The use as claimed in any of claims 15 to 17, characterized in that the antilipemic and the PDE inhibitor are present as a functional unit, in particular in the form of a mixture, a mix or a blend.
- 15 19. The use as claimed in any of claims 15 to 17, characterized in that the antilipemic and the PDE inhibitor are present (spatially) separated, in particular as a kit-of-parts.
20. The use as claimed in any of claims 15 to 19, characterized in that the antilipemic is selected from the compounds defined in claims 7 to 10.
- 20 21. The use as claimed in any of claims 15 to 20, characterized in that the PDE inhibitor is selected from the compounds defined in claims 11 to 14.

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